

## APPARATUS AND METHOD FOR MANUFACTURING MICRONEEDLES

### BRIEF DESCRIPTION OF THE INVENTION

Apparatus and methods are disclosed for manufacturing a microneedle array consisting of spaced-apart microneedles integral with and extending above a base sheet. A channel is formed extending from the tip of the microneedle through the base allowing fluids to pass completely through the microneedles in the array.

5 Prior art patents document the uses to which such microneedles are intended to be put and demonstrate known efforts to manufacture microneedles. In particular, United States Patents 6,471,903, 6,451,240, 6,379,324, 6,312,612 and 6,256,533, all 10 assigned to the Procter & Gamble Company describe in great detail the characteristics and uses of such microneedle arrays. To date, the manufacturing processes detailed in these references have proven less than satisfactory on a commercial scale.

Preferably, the microneedle array is made from a polymer with flow characteristics that will take on the shape of the mold form and allow channels to be 15 formed through the needles. Polymers such as urethanes, polysulfone, nylon, polycarbonates, acrylic and formulated radiation curable products may be used. The polymer may be applied in liquid form at a thickness of about 125 to 250 microns (.005 to .010 inches thick) and may be heat cured, or room temperature cured, ultraviolet cured or cured by other radiation wavelengths. An alternative method is to 20 apply the polymer as a film sheet then heat the polymer to a liquid state and cool back to a solid state once it has been formed with the gas channels.

One array of microneedles known to be of interest is formed with a height of about 160 microns (.0064 inches), a base diameter of about 50 microns (.002 inches),

and spaced with adjacent microneedles being about 300 microns (.012 inches) apart.

Preferably the center channel is formed as a through hole, tapered or constant diameter depending on the application required.

In the present invention, a mold assembly is separable into upper and lower  
5 manifolds. The lower manifold has a gas inlet communicating with an internal cavity  
and has a top surface with one or more ports communicating with the internal cavity.  
A gasket material is placed on the top surface of the manifold having apertures  
generally in register with the top surface ports. A gas-permeable sheet or membrane  
is placed on top of the gasket and, in a first embodiment of the invention, a layer of  
10 polymer is applied to the membrane above the ports.

The upper manifold is sized, shaped and adapted to be fluid tight attachable to  
the lower manifold and has an upper internal bore communicating at one end with the  
upper ports and at the other end with an exhaust gas port. A micro-structure mold  
form is positioned above the polymer layer. The mold form has cavities in the shape  
15 of the microneedles formed precisely thereon, preferably as a series of generally  
frustoconical sections. Each cavity has a hole formed centrally such that a gas-tight  
path is formed from the lower manifold through the mold form and into the upper  
manifold. The microneedle mold form may be of metallic or polymeric construction  
depending on the temperature requirements to cure the polymer to be formed into  
20 microneedles.

In use, after the liquid polymer to be formed has been applied between the gas  
permeable membrane and the mold form, the upper manifold is attached to the lower  
manifold and gas under pressure is directed through the lower manifold inlet to  
pressurize the polymer and force it into the mold form. It has been found that if the

gas pressure is maintained before the polymer in the mold form cures, the gas forces its way through the polymer and through the mold form holes, thereby forming channels which extend through the molded microneedles, from the base through the tip of each section, exiting through the top opening of the mold form.

5       Depending on the viscosity of the polymer to be formed, the gas pressure may range from less than 1 kilopascal per square centimeter (1 pound per square inch) to as much as 15-20 kilopascals per square centimeter (15-20 pounds per square inch). In some case it may be possible to use ambient air which has been filtered and dehumidified as the process gas. If UV or other radiation curable polymers are used it  
10      is anticipated that the use of inert gas may be of some advantage.

In another variation of the invention a thermoplastic film is substituted for the liquid polymer. The film is liquefied by heat, and then allowed to cool and solidify again after taking on the shape of the mold form and having channels formed through the microneedles.

15       Yet another variation of the invention substitutes a polymer powder for the liquid polymer. The powder is liquified by heat, then cooled and solidified after taking of the shape of the mold form and having channels formed through the microneedles.

Another embodiment uses a combination of gas pressure at the inlet of the  
20      manifold and vacuum pressure at the outlet side to draw gas through the polymer forming the channels.

When a UV-curable polymer is used, the upper manifold can be formed with transparent or translucent sections to allow such polymers to be exposed to ultraviolet light or other wavelengths while still in the mold form. After the polymer has set and

has cured, the manifold halves are separated and the cured polymer sheet, with the molded microneedles, is removed.

In another embodiment of the present invention, a support sheet is formed from a rigid material such as sintered brass, porous Teflon or other porous materials 5 allowing the gas to pass from the lower manifold to the gas permeable membrane while supporting the mold and polymer substrate.

In yet another embodiment, a second membrane is disposed in the upper manifold to absorb and collect excess polymer that may be extruded through the mold holes during the manufacturing process.

10 While the following describes a preferred embodiment or embodiments of the present invention, it is to be understood that this description is made by way of example only and is not intended to limit the scope of the present invention. It is expected that alterations and further modifications, as well as other and further applications of the principles of the present invention will occur to others skilled in 15 the art to which the invention relates and, while differing from the foregoing, remain within the spirit and scope of the invention as herein described. For the purposes of the present disclosure, two structures that perform the same function within an environment described above may be equivalent structures.

#### BRIEF DESCRIPTION OF THE DRAWINGS

20 These and further objects of the present invention will become apparent upon consideration of the drawings in which:

Fig. 1 is a perspective view of an apparatus for the manufacture of microneedle arrays showing the upper and lower manifold attached one to the other;

Fig. 2 is a perspective view of the lower manifold separated from the upper

manifold;

Fig. 3 is a perspective view of the lower manifold with the gasket in place;

Fig. 4 is a perspective view of the lower manifold showing a gas permeable membrane placed on the gasket and a layer of polymer placed on the membrane;

5 Fig. 5 is a perspective view of the mold form having the microneedle array pattern formed thereon seen next to the lower manifold;

Fig. 5A is a magnified side view of the mold form;

Fig. 6 is a perspective view of the mold form positioned upon the lower manifold;

10 Fig. 7 is a perspective view of the upper and lower manifolds reassembled one to the other and with a gas supply line connected to the lower manifold;

Fig. 8 is a sectional schematic view of the lower manifold with the gasket, membrane, polymer and mold form in place;

15 Fig. 9 is a sectional schematic view showing the upper and lower manifolds assembled together and the polymer in the mold form after the process has been carried out and the polymer is curing;

Fig. 10 is a sectional schematic view of an alternative method showing the upper and lower manifolds assembled together and the polymer in the mold form after the process has been carried out and the polymer is curing;

20 Fig. 11 is a partial perspective view of a single microneedle; and

Fig. 12 is a top schematic view of a support pad formed with a regularly spaced array of through holes.

Fig. 13 is a schematic view of a cylindrical flexible mold form of multiple microneedle array patterns joined to form a continuous belt.

Fig. 14 is a schematic view of the apparatus using the cylindrical mold in Fig. 12 to continuously fabricate product.

### DETAILED DESCRIPTION OF THE INVENTION

Referring now to Fig. 1, the numeral 10 indicates generally a mold assembly having a lower manifold 12 and an upper manifold 14. Attached fluid tightly to lower manifold 12 is a gas inlet coupling 16 and in like fashion, a gas outlet coupling 18 is attached fluid tightly to upper manifold 14.

Referring now to Fig. 2, lower manifold 12 is seen separated from upper manifold 14. Lower manifold 12 has a top surface 20 through which a pair of gas ports 22, 24 are drilled communicating with an inner, hollow inlet bore 26 shown schematically in Fig. 8. Bore 26 extends to communicate with a gas inlet 28 to which coupling 16 is attached.

Referring now to Fig. 3, a gasket material 30 is placed on top surface 20 of lower manifold 12. In the embodiment shown in Fig. 3, pad 30 is formed from silicone rubber and has pad openings 32, 34 sized and positioned to align with ports 22 and 24.

Referring to Fig. 4, a gas permeable membrane 36 is shown positioned on pad 30. Membrane 36 can be formed from a variety of gas permeable materials such as fabrics, meshes, sintered metals and the like. In a preferred embodiment of the present invention polyester fabric is used.

As further seen in Fig. 4, a selected quantity of polymer 38 is deposited on membrane 36 prior to the reassembly of mold 10. Polymer 38 can be selected from a number of known polymers such as urethane and can be supplied in forms as diverse as extruded films, powders, liquid solutions and UV ultraviolet curable solutions so

long as these polymer variations retain flow characteristics which allow the polymer to fill the mold form to flow under pressure. Preferably these physical characteristics are present at room temperature and the selected polymer can thereafter be cured to retain its molded shape. Curing can be accomplished by elevated mold temperature,  
5 exposure to ultraviolet radiation, cooling of molten polymer or other commonly known process expedients.

Referring now to Fig. 5 a mold form 42 is shown next to lower manifold 12. Manifold 12 is shown as in Fig. 3, with support pad 30 and pad openings 32, 34 positioned thereon. In the embodiment herein described, mold form 42 has  
10 microneedle array patterns 44 formed therein, preferably over those portions of mold form 42 that register with openings 32, 24. In other embodiments, array 44 is molded as a repeating pattern covering the entire surface of mold form 42. Manufacture of the precision patterns required to successfully mold microneedles is represented in the prior art by U.S. Patents 4,601,861, 4,478,769 and 4,486,363 all of which teach  
15 techniques for forming precision patterns in polymeric sheets.

Referring to Fig. 5A, there is shown a magnified side view of mold form 42 showing microneedle cavities 44 with openings at the top 45 and bottom 46.

Referring now to Fig. 6, mold form 42 is shown positioned on gasket or pad 30 with arrays 44 aligned with apertures 32, 34. As described above, apertures 32, 24  
20 are aligned with ports 22, 24 respectively.

Practice of the present invention may now be described by referring to Figs. 7, 8 and 9. After polymer 38 is placed on membrane 36 and mold form 42 is positioned over membrane 36, mold 10 is reassembled as shown in Fig. 7 with upper manifold 14 reattached to lower manifold 12 and with gas supply line 40 attached to gas inlet

coupling 16.

Fig. 8 is a schematic cross sectional view of lower manifold 12 of mold 10. Lower manifold 12 is shown with gasket pad 30 positioned upon top surface 20, with ports 22 and 24 aligned with gasket openings 32 and 34. Membrane 36 is positioned 5 atop gasket pad 30 and polymer 38 has been deposited upon membrane 30 above aligned ports and openings 22, 32 and 24, 34 respectively. Mold form 42 with microneedle pattern arrays 44 is positioned above polymer 38.

In a preferred embodiment, the microneedle pattern array 44 comprises a series of spaced-apart frustoconical cavities 46 which, in the present invention, 10 correspond to the size and shape of the microneedles to be formed.

Referring now to Fig. 9, mold 10 is shown assembled and in schematic cross section. After mold 10 has been sealed, gas is introduced via gas line 40 to gas inlet 28, passing through bore 26 and forced under pressure through ports 22, 24 and pad openings 34, through membrane 36 into contact with polymer 38. Polymer 38, when 15 introduced to mold 10 is in a flowable state and the gas forces polymer 38 into mold form 42, filling the microneedle cavities in array 44 and forming a series of channels 50 by displacing the polymer and exiting through mold form holes 52 into upper manifold ports 52, 54 and an upper mold bore 56, thereby, exiting mold 10 by gas outlet 48, to which gas outlet coupling 18 is attached. The gas flow is maintained 20 until polymer 38 is cured, making channels 50 permanent.

Referring now to Fig. 10, as an alternative method to the apparatus in Fig. 9, mold 10 is shown assembled and in schematic cross-section. After mold 10 has been sealed, gas is introduced via gas line 40 to gas inlet 28, passing through bore 26 and forced under pressure through ports 22, 24 and pad openings 34, through membrane

36. Polymer 38, when introduced to mold 10 is in a flowable state and occupies the cavities of the mold form 42. In this case the mold form 42 is inverted, so the larger opening appears at the top of the tapered cavity section, as illustrated in the enlarged view of Fig. 10. In this case it may not be necessary to utilize the upper manifold 14.

5 The gas forces a series of channels 50 by displacing the polymer and exiting through holes 52 at the top of the polymer into upper manifold ports 52, 54 and an upper mold bore 56, thereby exiting mold 10 by gas outlet 48, to which gas outlet coupling 18 is attached. The gas flow is maintained until polymer 38 is cured, making channels 50 permanent. Mold 10 is then separated and the cured polymer 38 having an array of

10 microneedles formed thereon is removed therefrom.

While the channels 50 appear to be uniform in size from top to bottom, in actual practice, dependent upon the viscosity of the polymer and the gas pressure, the channel may change in diameter to complement the mold shape.

Fig. 11 is a single molded microneedle 58 from the array shown having side walls 60 and a central opening 62 which is the uppermost portion of channel 50. The wall thickness of microneedle 52 can be varied by varying the rate of flow of the gas through polymer 38 as well as by varying the viscosity of the polymer 38.

Referring to Fig. 12, numeral 64 includes a second preferred embodiment of a support pad formed as a rigid metallic strip having a series of holes 66 formed therethrough, the size and spacing of holes 66 is thought to make the process of forming microneedles 58 more efficient.

The gas used in the foregoing process may be filtered in dehumidified air at ambient temperature. Under some circumstances, using certain polymers, such as UV curable polymers it is thought that using an inert gas such as nitrogen will be more

efficient.

Referring to Fig. 13, numeral 81 is a cylindrical mold form comprised of microneedle array patterns joined together to form a continuous belt.

Referring to Fig. 14, numeral 80 illustrates a form of apparatus which may be used to continuously fabricate microneedle products. The apparatus may comprise a variation of a double-belt press similar to that sold by Hymmen GmbH of Bielefeld, Germany, as models ISR and HPI, which are examples of continuous press, high-pressure processing machinery. By incorporating a generally cylindrical flexible mold 81 shown in Fig. 13 with a porous backing 82, polymer film 83 is introduced into the machine and melted to a fluid state by hot air plenum 84 beneath a lower porous belt 87. After fluidizing the polymer 83, the hot air from plenum 84 then forces air channels 50 through the polymer 83 which exits as a through channel 52 at the top side of the polymer. It further vents through the top porous mold backing 82. The gas flow is maintained until polymer 83 is cured, making channels 50 permanent.

Cured polymer 85 having an array of microneedles formed thereon is then separated from mold 81 and wound into rolls 86 with an interlayer of foam (not shown) to protect the microneedles. In a later operation the product is then cut into discrete sections.

In the foregoing description, it will be readily appreciated by those skilled in the art that modifications may be made to the inventions without departing from the concepts disclosed herein. Such modifications are to be considered as included in the following claims.